## REMARKS

Claims 1-68 have been cancelled and new claims 69-193 presented.

Support for the amendment to paragraph 14 can be found in original claim number 47, on page 112 of the instant application. Support for the amendment to paragraph 17 can be found in original paragraph 62, on page 25 of the specification, and in paragraph 72 on page 30. Support for the amendment to paragraph 18 can be found in original claim 41, page 110, original claim 60, page 115, original claim 65, page 116, and in original claim 22, page 105. Support for the amendment to paragraph 169 can be found in paragraph 168 on page 91of the specification.

Support for new claim numbers 92-102 can be found in original claim number 22 on page 105 of the instant application. Support for new claim numbers 123-132 can be found in original claim 41 on page 109. Support for new claim numbers 152-161 can be found in original claim 60, page 115. Support for new claim numbers 180-189 can be found in original claim 65, page 116. Support for new claim numbers 138 and 166 can be found in original claim 47, on page 112. Support for new claim numbers 139 and 167 can be found in the instant application in paragraph 62 on page 25 and in paragraph 72 on page 30.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attachment is captioned "Version with markings to show changes made." No New Matter has been added by way of this amendment.

## *Conclusion*

Examination on the merits is respectfully requested.

Respectfully submitted,

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The following paragraphs have been amended to replace the original paragraphs having the same number.

14. In its broadest aspect, the invention is directed to a method for delivery of a therapeutic agent or a diagnostic agent from an initial bodily compartment to at least one target bodily compartment, the method carried out by at least administering to the initial bodily compartment an effective transcompartmental delivery promoting amount of one of the following conjugates:

a) a polymer having multiple functional groups at least one of which is covalently bound to a therapeutic or diagnostic agent, and at least one cell uptake promoter is covalently bound to the therapeutic or diagnostic agent; or

b) a polymer and at least one cell uptake promoter bound thereto; the polymer further comprising multiple functional groups at least one of which is covalently bound to a therapeutic or diagnostic agent.

The conjugates described above include compounds having the general formulas:

a) $(X)_o$-$(Y)_m$-$(\text{linker})_n$

where X is one or more transporter, receptor, binding or targeting ligands, including retro inverso peptides, which may be identical or non-identical;

where Y is one or more of any therapeutic or diagnostic moieties, naturally occurring or artificial, including retro inverso peptides, which may be identical or non-identical;

where linker comprises polymer with functional groups and provides covalent bonds between linker and Y; and

m, n, and o may be any independently varying integers, or more specifically may each independently vary from 1 to about 100; or

b) $(Y)_m$-$(linker)_n$-$(X)_o$

where X is one or more transporter, receptor, binding or targeting ligands, including retro inverso peptides, which may be identical or non-identical;

where Y is one or more of any therapeutic or diagnostic moieties, naturally occurring or artificial, including retro inverso peptides, which may be identical or non-identical;

where linker comprises polymer with functional groups and provides covalent bonds between linker and X, and/or Y, or the combination thereof; and

m, n, and o may be any independently varying integers, or more specifically may each independently vary from 1 to about 100.

17. The [polymer] linker may be a linear or branched polymer, for example, poly(ethylene glycol), carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1,3-dioxolane, poly-1,3,6-trioxane, an amino acid homopolymer, polypropylene oxide, a copolymer of ethylene glycol/propylene glycol, an ethylene/maleic anhydride copolymer, an amino acid copolymer, [a] an amino acid copolymer of polyethylene glycol and an amino acid, a polypropylene oxide/ethylene oxide copolymer, and a polyethylene glycol/thiomalic acid copolymer. Poly(ethylene glycol) is preferred. Branched polyethylene glycol is most preferred. The [polymer] linker may have a molecular weight ranging from about 200 to about 200,000 Daltons; preferably 2,000 to about 50,000 Daltons, and most preferably about 10,000 Daltons. The multiple thiol compounds are attached to said polymer at an interval, preferably the interval is every about 100 to about 10,000 Daltons; most preferably it is about 300 to about 5,000 Daltons.

18. The cell uptake promoter, transporter, receptor, binding or targeting ligand may be a vitamin such as, but not limited to, biotin, pantothenate, vitamin B6, or vitamin B12, or analogs thereof. It may also be a carbohydrate for which a transporter exists, such as for glucose and glucose derivatives. It may also be a chemotactic peptide such as a formyl-methionyl peptide. Examples of other peptide targeting agents with a range of size and amino acid order includes the peptide formyl-methionyl-leucyl-phenylalanine (fMLF) peptide and variants thereof which serves as a transport enhancing moiety and increases drug delivery into cells expressing the

receptor for that peptide. fMLF is only one example of the class of formyl-methionyl peptides that binds to this receptor. Other examples include other formylmethionyl peptides and proteins capable of binding to the formyl peptide receptor on the surface of phagocytic cells, which also has been reported to bind to certain other, unrelated peptides lacking the formylmethionyl moiety, and these latter peptides unrelated to formylmethionyl peptides but capable of binding to the receptor are fully embraced herein. Other transport enhancing moieties may include Tat-biotin, retro-inverso (RI)-Tat, and RI-TAT-biotin. It may be a chemokine, such as RANTES or IL-2. It may also be a peptide such as Tat, penetratin or VEGF, or a membrane fusion peptide such as gp41. It may also be an enzyme such as neuraminidase. It may be an antibody or an antibody fragment with specific affinity for lymphocyte subpopulations, neurons or other cell types. Examples of such antibodies include antibodies to CD4, which may target helper T-cells, or CD44, which may target ovarian cancer cells. It may also be an antigen or epitope such as influenza virus hemagglutinin. It may also be a hormone such as estrogen, progesterone, LHRH, ACTH or growth hormone. It may also be an adhesion molecule such as ICAM, NCAM or a lectin. It may also be a lipid, such as myristic acid or stearic acid. It may be an oligonucleotide or an antisense oligonucleotide such as aptamers containing 5-(1-pentyl)-2'-deoxyuridine. These are merely non-limiting examples. Any of the cell uptake promoters embraced herein may be provided as a form which is capable of being covalently attached to a polymer or therapeutic agent as described above, such as through a functional or reactive group on the cell uptake promoter or by a chemical modification to provide one.

169. Injection of PEG/A-fMLF[4]$_4$-DIG[4]$_4$ into the peritoneal cavity of BALB/c mice was used to determine the in vivo properties of this conjugate, in contrast to using the differentiated HL-60 cell line. The mice in this study were not injected with thioglycol, and, therefore, the macrophages in the peritoneal cavity were not activated. These non-activated peritoneal cells accumulated DIG to about a 5-fold greater extent from the targeted conjugate, PEG/A-fMLF[4]$_4$-DIG[4]$_4$, than from the non-targeted conjugate, PEG/A-DIG[4]$_8$ (Figure 15). In fact, 17% of the administered PEG/A-fMLF[4]$_4$-DIG[4]$_4$ was taken up by peritoneal cells, whereas they accumulated only 3.3% of the non-targeted PEG/A-DIG[4]$_8$. This low level of accumulation of non-targeted DIG is not surprising, since we have shown that in culture there is some nonspecific binding of PEG/A to promyelocytic HL-60 cells (Figure 24). Peritoneal incubation for less than

1 h (15 or 30 min) gave similar results. It should be noted that the DIG that was accumulated in cells is expected to remain conjugated to its PEG/A carrier, but this was not confirmed.